STATISTICAL REVIEW AND EVALUATION

NDA #: 20-920 Major Amendment
Applicant: Scios Inc.
Drug Name: Natrecor (nesiritide)
Indication: decompensated congestive heart failure
Document Reviewed: desk copy for biostatistician – Volume 1 (January 9, 2001), SAS data sets (December 29, 2000 and April 2, 2001), electronic submission to major amendment (CDER REC'D Date: March 2, 2001), Minor amendment (document N-BZ, CDER REC'D Date: March 29, 2001), Minor amendment (document N-BZ, CDER REC'D Date: April 2, 2001), Briefing document (CDER REC'D Date: April 4, 2001)

1. INTRODUCTION

This submission provides a major amendment in response to the Agency's April 27, 1999 non-approval letter for Natrecor NDA 20-920. According to the sponsor, the non-approval letter did not question the efficacy of Natrecor as demonstrated by the data submitted in the NDA. To support the approval, the Agency requested a double-blind, randomized, active-, and placebo-controlled study to address the concerns outlined in the sponsor's letter of January 9, 2001. Following a number of meetings or teleconferences between the sponsor and the Agency, the sponsor conducted the VMAC (Vasodilation in the Management of Acute Congestive Heart Failure) trial. This review pertains to this trial.

2. OVERVIEW OF VMAC TRIAL

The 55-center, randomized, double-blinded clinical trial was designed to compared the hemodynamic, clinical, and safety effects of the addition of Natrecor, placebo, and IV nitroglycerin to standard care (diuretics, dobutamine, dopamine, or other long-term cardiac therapies) in patients requiring hospitalization for the treatment of dyspnea at rest due to acutely decompensated congestive heart failure.

Randomization of approximately 480 patients was to be stratified by the investigators' clinical decision to use a right heart catheter to the patients. Approximately 240 catheterized patients were to be randomized in a 1:1:2:2:2 ratio to one of five treatment groups: 3 hours placebo followed by IV nitroglycerin, 3 hours placebo followed by Natrecor fixed dose, IV nitroglycerin, Natrecor fixed dose, Natrecor adjustable dose. Approximately 240 patients non-catheterized patients were to be randomized in a 1:1:2:2 ratio to one of the four treatment groups: 3 hours

placebo followed by IV nitroglycerin, 3 hours placebo followed by Natrecor fixed dose, IV nitroglycerin, Natrecor fixed dose. During the placebo-controlled period, comparisons were made among three groups: nitroglycerin, Natrecor, and placebo. The two Natrecor treatment groups (fixed dose and adjustable dose) were pooled for the analysis during the placebo-controlled period. The 3-hour time point has a window of ±90 minutes. During the active-controlled or post-treatment period, overall comparisons of catheterized and non-catheterized patients were made between all nitroglycerin and all Natrecor and between all nitroglycerin and Natrecor fixed dose.

Study drug was to be administered for at least 24 hours. The first 3 hours were placebo-controlled and nitroglycerin-controlled. At the end of 3 hours, placebo patients crossed over to double-blinded therapy with a titration regimen of nitroglycerin or Natrecor fixed dose. For the first 3 hours, Natrecor/placebo was administered as a 2-µg/kg bolus, followed by a fixed-dose infusion of 0.01 µg/kg/min. For Natrecor adjustable-dose group, after 3 hours, the Natrecor dose could be increased at 3-hour intervals if the subject had an SBP >= 100 mm Hg and a PCWP >= 20 mm Hg at the time of the dose increase. The regimen included a 1-µg/kg bolus, followed by an increase in the infusion dose by 0.005 µg/kg/min above the previous infusion dose, up to a maximum dose of 0.03 µg/kg/min. All doses of Nitroglycerin/placebo were determined by the Investigator. Nitroglycerin/placebo was to be titrated to achieve the desired clinical effects.

During the first 3-hour period, in catheterized patients only, PCWP and PAP were measured at 15 minutes, 30 minutes, 1 hour, 2 hours, and 3 hours. Cardiac ouput (CO) and MRAP were measured at 1 and 3 hours. In all subjects, vital signs and symptoms (dyspnea and global clinical evaluations) were assessed at 15 minutes, 30 minutes, 1, 2, and 3 hours. After 3 hours, in catheterized patients only, PCWP and PAP were obtained at 6, 9, 12, 24, 36, and 48 hours, and when study drug was discontinued before 48 hours. If the Natrecor dose was increased, PCWP and PAP were measured immediately before and 1 hour after each dose increase. In all subjects, vital signs were assessed every 3 hours and frequently for the first 2 hours after any dose changes, discontinuation, or restarting of the infusion. Dyspnea and global clinical evaluations were obtained at 6 and 24 hours and at the time of discontinuation of study drug. Each patient independently was to evaluate his/her dyspnea and global clinical status at each time point without help from investigators or study staff. If the patient was catheterized, sympotoms were to be collected bofore the hemodynamic measurements were obtained at

each time point. The hemodynamic results were not to be discussed with the patient or within the hearing of the patient.

Mortality was assessed through 6 months. Three time points specified were 30 days, 90 days and 6 months. General adverse events were assessed through study day 14.

Endpoints

The primary endpoints were the changes from baseline, 3 hours after the start of study drug, in PCWP for catheterized subjects and in the subject's self-evaluation of dyspnea for all subjects. The secondary endpoints included the effect on PCWP and dyspnea 1 hour after the start of study drug, the onset of effect on PCWP, the effect on PCWP 24 hours after the start of study drug, and the overall safety profile.

Statistical analysis method

The main contrast is that between Natrecor and placebo. The primary efficacy parameter, the mean change from baseline in PCWP at 3 hours, was to be analyzed with ANOVA. A non-parametric Kruskal-Wallis test was also to be performed to check the robustness of the primary efficacy results. Another primary efficacy parameter, the subject's dyspnea evaluation at 3 hours, was represented at a 7-point ordinal response relative to baseline status (score: markedly better (3), moderately better (2), minimally better (1), no change (0), minimally worse (-1), moderately worse (-2), markedly worse (-3)). The primary analysis was based on ANOVA. A stratified two-sample Wilcoxon procedure (van Elteren's test), stratified on right heart catheter use, was also to be performed at a two-sided alpha $\alpha = 0.05$. According to the study report, this analysis was pre-specified as a supplemental analysis to test the robustness of the primary analysis and was recommended by the Agency as a more appropriate analysis (FDA meeting minutes dated 02/10/2000). The reason given in the study report is that a skew distribution toward more patients being improved as a result of standard care during the 3 hours would be expected in the placebo group.

There was no plan for alpha adjustment for the two primary endpoints because both primary endpoints must reach statistical significance.

Mortality was analyzed using a stratified log-rank test with catheter as a stratification factor.

Sample size planning

For the 3-hour dyspnea evaluation, the sample sizes of 200 and 140 for the Natrecor and placebo arms, respectively, were thought to have 88% power to detect a 0.3-point difference between the two groups using two-sample t-test at the two-sided 0.05 significance level, assuming a common standard deviation of 0.8. The two-sample Wilcoxon procedure would have approximately 86% power to detect a treatment difference in the following proportion:

Trt group	Markedly improved	Moderately improved	Minimally improved	unchanged	Minimally worsened	Moderately worsened	Markedly worsened
Natrecor	5%	20%	25%	40%	5%	5%	0%
Placebo	0%	15%	20%	50%	5%	5%	5%

For the 3-hour PCWP evaluation, the sample sizes of 120 and 60 catheterized patients for the Natrecor and placebo arms, respectively, would have 88% power to detect a 1.86 mm Hg difference between the two groups using two-sample t-test at the two-sided 0.05 significance level, assuming a common standard deviation of 6 mm Hg.

Baseline characteristics and clinical presentation

There appeared to be some imbalance with respect to clinical presentation at baseline between the nitroglycerin group and the other two groups (Table 1).

Table 1. Baseline characteristics and clinical presentation between placebo-controlled treatment groups

	Nitroglycerin (N=143)	Natrecor (N=204)	Placebo (N=142)	p-value
Gender				0.030
Male	86 (60%)	148 (73%)	103 (73%)	
Female	57 (40%)	56 (27%)	39 (27%)	
Age				0.22
< 65 yrs	88 (62%)	118 (58%)	73 (51%)	
≥ 65 yrs	55 (38%)	86 (42%)	69 (49%)	
Race				0.98
Caucasians	85 (59%)	118 (58%)	83 (58%)	
Blacks	35 (24%)	50 (25%)	34 (24%)	
Asians	3 (2%)	4 (2%)	1 (1%)	
Hispanics	19 (13%)	29 (14%)	21 (15%)	
Others	1 (1%)	3 (1%)	3 (2%)	
Cardiac History				
Sustained VT	9 (6%)	31 (15%)	22 (15%)	0.018
Frequent PVCs	41 (29%)	68 (33%)	57 (40%)	0.12
Longterm medications				
ACE inhibitors	76 (53%)	130 (64%)	88 (62%)	0.12
Nitrates	42 (29%)	80 (39%)	51 (36%)	0.17
Warfarin	48 (34%)	75 (37%)	37 (26%)	0.11
Class III antiarrhythmics	17 (12%)	41 (20%)	19 (13%)	0.08
Clinical presentation				
Baseline SBP< 100 mmHg	20 (14%)	48 (24%)	22 (15%)	0.067
IV vasoactive Rx* within 24 hours before study drug	22 (15%)	60 (29%)	35 (25%)	0.009
Baseline dobutamine	11 (8%)	33 (16%)	25 (18%)	0.023
Baseline dopamine	2 (1%)	15 (7%)	5 (4%)	0.023

Efficacy Results

1) 3-hour PCWP (primary endpoint)

As shown in Table 2, Natrecor decreased PCWP at the 3-hour time point to a significantly greater degree than placebo ($p < 0.001$).

Table 2. Mean change (±se) from baseline in 3 hour PCWP (All treated catheterized subjects, as randomized)

	Nitroglycerin (N=60)	Natrecor (N=124)	Placebo (N=62)
# of subjects analyzed	59	121	62
Mean change (±se) from last baseline	-3.8 ± 0.7	-5.8 ± 0.5	-2.0 ± 0.7
p-value compared to placebo	0.087	< 0.001	----
p-value Natrecor vs. NTG		0.027	
Mean change (±se) from average baseline	-3.9 ± 0.7	-5.9 ± 0.5	-1.9 ± 0.7
p-value compared to placebo	0.045	< 0.001	----
p-value Natrecor vs. NTG		0.031	

Reviewer's analysis

The PCWP response profile over time through 3 hours also showed that Natrecor decreased PCWP significantly more than placebo throughout the three hours (see the sponsor's Table 13, page 63 of clinical final report). Effects on other hemodynamic parameters were no surprise (see the sponsor's Figure 6 and Table 14, clinical final report).

2) 3-hour dyspnea evaluation

One patient (#357401) in the Natrecor group did not have any dyspnea or global evaluations at any time point due to the reason that he fluctuated in and out of a confused state, according to the sponsor's explanation. In the analysis, this patient was not included.

At the request of Dr. Karkowsky, this reviewer examined the patients who had PCWP measured prior to dyspnea assessment. There is no great disparity of recording time difference that might induce bias in favor of Natrecor for dyspnea analysis (see Table 3).

Table 3. Difference (in minutes) between time of 3-hour PCWP measurement and time of 3-hour dyspnea assessment

	Nitroglycerin (N=60)	Natrecor (N=124)	Placebo (N=62)
PCWP time < dyspnea time (n; mean±sd in min)	1 ; -2 ±.	14; -5 ±4	13; -8 ±13
PCWP time >= dyspnea time (n; mean±sd in min)	58; 3 ±5	106; 3 ±5	49; 2 ± 4

Reviewer's analysis

Based on Table 4, Natrecor was seemingly associated with a more favorable dyspnea evaluation score or a greater percentage of subjects whose dyspnea was improved overall at 3 hours than placebo (nominal p-value = 0.050 (ANOVA), 0.034 (van Elteran's non-parametric test)). ANOVA is primary and the non-parametric analysis is a pre-specified supplementary analysis.

Table 4. Subject's 3-hour dyspnea evaluation (All treated subjects as randomized)

	Nitroglycerin (N=143)	Natrecor (N=204)	Placebo (N=142)
# of subjects analyzed	143	203	142
Mean ±se	1.3 ± 1.1	1.3 ± 1.1	1.1 ± 1.2
p-value[1] compared to placebo	0.41	0.050	----
p-value[1] Natrecor vs. NTG		0.29	
Markedly better	17 (12%)	34 (17%)	25 (18%)
Moderately better	50 (35%)	54 (27%)	24 (17%)
Minimally better	37 (26%)	64 (32%)	41 (29%)
No change	33 (23%)	45 (22%)	46 (32%)
Minimally worse	5 (3%)	5 (2%)	6 (32%)
Moderately worse	0 (0%)	1 (0.5%)	0 (0%)
Markedly worse	1 (1%)	0 (0%)	0 (0%)
p-value[2] compared to placebo	0.19	0.034	----
p-value[2] Natrecor vs. NTG		0.57	

[1] based on ANOVA analysis [2] based on van Elteran's test

Reviewer's analysis

3) Subgroup results

Natrecor had a larger decrease in PWCP and a larger improvement in dyspnea score than placebo in most of the subgroups (Table 5).

Table 5. Subgroup results on 3-hour change from baseline in PWCP and 3-hour dyspnea assessment

	Nitroglycerin	Natrecor	Placebo
PCWP			
Male	43; -3.6±0.9	92; -5.9±0.7	47; -1.9±0.6
Female	16; -4.5±1.1	29; -5.5±1.0	15; -2.3±1.3
Caucasians	33; -2.6±0.9	74; -5.4±0.8	39; -2.2±0.6
Blacks	17; -5.9±1.1	30; -5.9±0.9	14; -0.6±1.2
Hispanics	9; -4.2±1.8	15; -7.0±1.5	8; -3.4±2.2
Others	1; -21	---	---
< 65 years old	40; -4.5±0.8	70; -6.2±0.8	37; -1.5±0.8
≥ 65 years old	19; -2.4±1.1	51; -5.3±0.9	25; -2.9±0.7
NYHA Class I	---	1; -5.0	---
Class II	10; -4.1±1.4	9; -5.2±1.3	2; -7.5±2.5
Class III	27; -4.7±0.9	48; -7.2±0.9	24; -2.0±0.9
Class IV	18; -1.4±1.3	54; -4.6±1.0	31; -1.0±0.6
No previous CHF	4; -8.0±2.4	9; -6.8±2.3	5; -6.8±2.4
Dyspnea			
Male	86; 1.1±0.1	147; 1.3±0.1	103; 1.0±0.1
Female	57; 1.4±0.1	56; 1.4±0.2	39; 1.4±0.2
Caucasians	85; 1.1±0.1	117; 1.1±0.1	83; 1.0±0.1
Blacks	35; 1.6±0.2	50; 1.7±0.1	34; 1.2±0.2
Hispanics	19; 1.4±0.3	29; 1.3±0.2	21; 1.4±0.3
Others	4; 1.3±0.3	7; 1.9±0.3	4; 0.5±0.3
< 65 years old	88; 1.2±0.1	118; 1.4±0.1	73; 1.2±0.1
≥ 65 years old	55; 1.3±0.1	85; 1.2±0.1	69; 1.1±0.1
NYHA Class I	1; 2.0	1; 2.0	1; 0.0
Class II	18; 0.8±0.2	13; 1.3±0.3	7; 0.9±0.5
Class III	57; 1.3±0.1	88; 1.3±0.1	59; 1.3±0.1
Class IV	55; 1.2±0.2	85; 1.2±0.2	64; 0.9±0.2
No previous CHF	12; 1.8±0.3	16; 1.8±0.3	11; 1.5±0.4

Reviewer's analysis

4) Summary

The VMAC study had two primary endpoints, PCWP and dyspnea. The rule for declaring that VMAC trial has a positive finding is that both endpoints must reach statistical significance (usually nominal two-sided p-values ≤ 5%). The largest p-value of the two endpoints is ≤ 0.05; thus, the VMAC trial reaches statistical

significance. The nominal p-value for dyspnea improvement is statistically significant.

Mortality

Mortality was not an efficacy endpoint. The study was not designed to rule out the excess risk of 50% possibly associated with Natrecor. The mortality data contain study day of last known alive and study day of last follow up for each patient. The distributions of time to censoring appeared to be comparable between Natrecor and nitroglycerin (Table 6).

Table 6. Distribution of time (in days) to censoring
(All treated subjects, as randomized)

	Nitroglycerin (N=216)	Natrecor fixed dose (N=211)	All Natrecor (N=273)
# of subjects analyzed	216	211	273
# of patients alive (%)	172 (79.6%)	165 (78.2%)	206 (75.5%)
Maximum	331	358	358
99th percentile	305	315	315
95th percentile	258	278	271
90th percentile	248	247	246
75th percentile	205	209	206
50th percentile	188	188	187
Mean	196	196	194
25th percentile	184	185	184
10th percentile	183	182	182
5th percentile	181	160	160
1st percentile	31	30	30
Minimum	30	30	6

Reviewer's analysis (using study day of last follow up)

Three time points specified for mortality analysis were 30 days, 90 days and 6 months. The results of the analyses using the two variables are very similar and also very similar to the sponsor's results. There was no statistically significant difference in mortality, which is not surprising since the study was not designed to show the treatment difference. Numerically, the Natrecor groups had a greater mortality risk than the nitroglycerin group (30 days hazard ratios are 1.41 and 1.56, 90 days hazard ratios are 1.44 and 1.52, 6-month hazard ratios are 1.11 and 1.22), see Table 7 and the sponsor's amended Figure 20,

Table 7. Mortality results of VMAC study
(All treated subjects, as randomized)

	Nitroglycerin (N=216)	Natrecor fixed dose (N=211)	All Natrecor (N=273)
# of subjects analyzed	216	211	273
30 days			
Death (%)	11 (5.1%)	15 (7.1%)	22 (8.1%)
p-value compared to nitroglycerin	----	0.39	0.23
Harzard ratio of Natrecor To nitroglycerin (95% CI)	----	1.41 (0.65, 3.07)	1.56 (0.75, 3.24)
90 days			
Death (%)	27 (12.5%)	37 (17.5%)	52 (19.1%)
p-value compared to nitroglycerin	----	0.15	0.078
Harzard ratio of Natrecor To nitroglycerin (95% CI)	----	1.44 (0.88, 2.37)	1.52 (0.95, 2.43)
6 months			
Death (%)	44 (20.4%)	46 (21.8%)	67 (24.5%)
p-value compared to nitroglycerin	----	0.62	0.32
Harzard ratio of Natrecor To nitroglycerin (95% CI)	----	1.11 (0.74, 1.68)	1.22 (0.83, 1.79)

Reviewer's analysis (using study day of last follow up)

According to the study report (Table 3-2 of briefing document), there appeared to be some baseline imbalance between the active-controlled treatment groups, Natrecor and nitroglycerin. More Natrecor patients were male, were receiving chronic therapy with a Class III antiarrhythmic medication, received an IV vasoactive medication within 24 hours before study drug, and had study drug added to ongoing therapy with dobutamine or dopamine. The Natrecor group also had more subjects with NYHA Class IV chronic CHF. More Natrecor patients has a history of significant ventricular arrhythmias. The results from Cox regression analysis containing these variables did not appear to change the hazard ratio greatly.

3. CONCLUSIONS

The VMAC clearly showed that Natrecor significantly decreased PWCP. Natrecor also showed a statistically significant symptomatic benefit with p = 0.034.

The excess risk of mortality associated with Natrecor in comparison to nitroglycerin is about 41%-56% in 30 days, 44%-52% in 90 days and 11%-22% in 6 months. The VMAC data did not rule out 50% excess risk of mortality (Table 7).

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Acting Team Leader

This review consists of 11 pages of text.

Concur: Dr. Chi

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/s/

James Hung
4/18/01 12:22:19 PM
BIOMETRICS

The review needs to get to HFD-110 division by April 23 because it wil
l go to AC meeting in May.

George Chi
4/19/01 11:10:44 AM
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